

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**215383Orig1s000**

**PRODUCT QUALITY REVIEW(S)**

## NDA/BLA OPQ Review and Evaluation

**Disclaimer:** In this document, the sections labeled as “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

**NDA 215383**

**Review # 01**

### OPQ RECOMMENDATION: APPROVAL

**Drug Substance Retest Period:** (b) (4) months at (b) (4).  
FDA Assessment: Retest date of (b) (4) months may be granted when stored at the proposed storage conditions

**Drug Product Expiration Dating Period:** 24 months at 20-25°C, excursions permitted as per USP.  
FDA Assessment: An expiration dating period of 24 months may be granted when stored at the proposed storage conditions.

[Applicant will complete this section.]

Drug Name/Dosage Form	Belzutifan Tablet
Strength	40 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Indication	treatment of patients with von Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC), not requiring immediate surgery.
Applicant	Merck Sharp and Dohme Corp.
US agent, if applicable	

[FDA will complete these sections.]

Submit Date(s)	01/15/2021
Received Date(s)	01/15/2021
PDUFA Goal Date	09/15/2021
Division/Office	DO1/OHOP
Review Completion Date	07/28/2021

<b>Established Name</b>	belzutifan
<b>(Proposed) Trade Name</b>	WELIREG™
<b>Pharmacologic Class</b>	Belzutifan is an inhibitor of hypoxia-inducible factor-2 $\alpha$ (HIF-2 $\alpha$ ).
<b>Recommendation on Regulatory Action</b>	Approval

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD06	01/15/2021	All: DS/DP/OPMA/Biopharm/NIR ID
SD10	02/19/2021	DP/OPMA/Biopharm
SD17	03/09/2021	DP/OPMA
SD21	03/25/2021	DS
SD23	03/29/2021	OPMA
SD26	04/02/2021	DP/Biopharm
SD27	04/14/2021	NIR ID test
SD30	04/20/2021	DP
SD31	04/21/2021	DP/OPMA
SD38	05/07/2021	OPMA/NIR ID
SD41	05/13/2021	DS
SD51	06/10/2021	DP/OPMA
SD53	06/15/2021	DP/OPMA
SD60	06/30/2021	DP/Biopharm
SD70	07/07/2021	Biopharm
SD78	07/13/2021	Biopharm

## Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Rajan Pragani	Paresma Patel
Drug Product	Nina Ni	Anamitro Banerjee
Process and Facility	Abdullah Md Mahmud	Rakhi Shah
NIR ID test	Yifan Wang	Bogdan Kurtyka
Biopharmaceutics	Gerlie Gieser	Banu Zolnik
Regulatory Business Process Manager	Kristine Leahy	
Application Technical Lead	Xiao Hong Chen	
ORA Lead	Caryn McNab	
Environmental	Nina Ni	Anamitro Banerjee

## ORBIS Partner Agency Quality Review Team

Agency	PRIMARY REVIEWER	SECONDARY REVIEWER
HC Canada		
MHRA Great Britain		
TGA Australia		

## RELATED/SUPPORTING DOCUMENTS

### DMFs:

[Applicant will complete]				[FDA will complete]	
DMF #	Type	Holder	Item Referenced	Status	Comments
(b) (4)	III		(b) (4)	Adequate	See note *
	III			Adequate	See note *
	III			Adequate	See note *
	III			Adequate	See note *
	III			Adequate	See note *
	III			Adequate	See note *
	III			Adequate	See note *

\*Note: No review is needed per OPQ policy

**Other Documents:** *No other documents.*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	137354	Belzutifan for the treatment of VHL disease-associated renal cell carcinoma
IND	132120	(b) (4)

## CONSULTS

None

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## Evaluation of the Quality Information

[Applicant to provide link to the data in m3 sections as appropriate]

### DIFFERENCES IN M3 MODULE IN SUBMISSIONS TO DIFFERENT AGENCIES

[To the Applicant: Insert text here.] Report any changes in formulation, manufacturing, container closure system, presentation, etc. **Do not include labeling differences.**

#	TGA (Australia)	HC (Canada)	MHRA (Great Britain)	FDA (US)
P.3.1	Packaging Site (Merck Sharp and Dohme BV, Netherlands)	Packaging Site (Merck Sharp and Dohme BV, Netherlands)	Packaging Site (Merck Sharp and Dohme BV, Netherlands)	Packaging Site (Merck Sharp and Dohme Corp, USA)

### 1. EXECUTIVE SUMMARY

The applicant submits a 505b1 NDA for belzutifan (MK-6482; formerly PT2977) immediate release tablets for the treatment of patients with von Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC), not requiring immediate surgery. The indication that the applicant was seeking to approve has been granted breakthrough designation and orphan drug status. Belzutifan is a potent, orally active, small molecule inhibitor of HIF-2 $\alpha$ , with potential antineoplastic activity. The recommended daily dose is 120 mg (three 40 mg immediate release [IR] tablets), once daily with or without food. The efficacy and safety of MK-6482 monotherapy for treatment of patients with VHL disease-associated RCC was established on a Phase 2 single arm study MK-6482-004 (formerly PT2977-202) (61 participants).

#### Drug Substance

The drug substance is manufactured (b) (4). Polymorph screen experiments demonstrated no other crystalline forms of belzutifan except for (b) (4). The drug substance is not hygroscopic. The solubility in water or other aqueous buffers is practically insoluble. The drug substance manufacturing process changes between different API manufacturers used from clinical trials to commercial production appear minor in nature between the (b) (4) different processes (b) (4). Overall, the manufacturing processes and impurity profiles appear comparable between the different API suppliers. The drug substance is (b) (4), so (b) (4) and particle size distribution (PSD) are not considered critical quality attributes for the drug substance. The drug substance specifications are based on ICH Q3A, Q3C and Q3D, and specified



impurities qualification has been found acceptable by the pharm/tox reviewer. A thorough risk assessment for potential mutagenic impurities was conducted by the applicant consistent with ICH M7 and was assessed by pharm/tox reviewer and deemed acceptable. No potential mutagenic impurity was routinely tested in the process or in the final drug substance specification. A (b) (4) month retest date for the drug substance stored at (b) (4) supported by 12 month long term and 6 month accelerated stability data was found acceptable.

### Drug Product

The belzutifan tablets are intended for oral administration in 40 mg dosage strength, which are blue, oval shaped tablets, debossed with markings "177" on one side, and film coated for immediate release oral administration. The drug product strength is expressed as the free form. All excipients are compendial/composed of compendial excipients except for FD&C Blue #2 aluminum lake which complies to 21 CFR 74.102 & 82.51. The composition of the formulation remained unchanged across batches manufactured to support pivotal clinical trials and FSS (formal stability studies, i.e., same as FMF) as well as the commercial drug product (FMI) --- except for debossing of the tablet for commercial production. The proposed drug product is considered as a (b) (4). However, belzutifan drug substance, crystalline (b) (4) is (b) (4) to facilitate bioavailability of the drug. The drug product is packaged in HDPE bottle with 90 counts. The drug product specifications are proposed per ICH guidelines and found acceptable. Based on available 12 month long term stability data, a 24 month expiry was proposed and found acceptable.

### Process and Facility

The drug product manufacturing process consists of (b) (4)

The proposed commercial manufacturing process will utilize equipment of similar design and operating principle and similar manufacturing controls that were used in the FSS and site stability batch. (b) (4)

Uniformity of dosage units by stratified sampling was neither performed in any exhibit batches nor proposed for the commercial batches based on low risk. (b) (4)

The proposed hold time is supported by acceptable hold stability data. A bulk tablets hold time of (b) (4) months was proposed and found acceptable based on hold time study results. The applicant acknowledged that the manufacturing start date is at the (b) (4). Therefore, both hold times will not be extra and are included in the expiration dating period.

All manufacturing and controls facilities are deemed acceptable based on compliance status and prior history except the drug product manufacturing facility, MSD International GmbH, Ireland which was considered high risk because the (b) (4) manufacturing process is new to the facility with no prior inspectional coverage. Due to

the pandemic, a preapproval inspection (PAI) could not be performed, the 704(a)4 document review was performed in lieu of PAI. Based on the joint 704a4 assessment between OPMA and ORA, the site is found adequate and recommended for approval.

### Biopharmaceutics

The applicant is not proposing formal FDA classification, but has classified belzutifan as BCS Class II. The Biopharmaceutics reviewer agrees based on data provided. The drug product dissolution characteristics demonstrates pH-dependent dissolution: very rapid (>85% in 15 min) in the proposed dissolution medium (pH 6.5) and in pH 7.5 buffer, but incomplete (<30%) in water, 0.1N HCl, and pH 4.5 acetate buffer. The proposed dissolution method and acceptance criteria (USP apparatus 2, paddle speed 50 rpm, medium volume 900 mL,  $Q = \frac{(b) (4)}{(4)}\%$  in 15 min.) were found acceptable. The method has discriminating power for changes/differences in quality attributes (e.g., level of tablet  $(b) (4)$ ,  $(b) (4)$  process parameter), and shows the expected rank-order relationship between dissolution rate & levels of API  $(b) (4)$  material,  $(b) (4)$  content, and tablet hardness. The method achieves complete dissolution and maintains sink conditions & analyte stability with no coning. The bridging between the clinical formulation and the proposed commercial formulation is deemed acceptable based on intro and in vivo data.

### Conclusion

The OPQ review team found that the CMC information in the NDA acceptable. All manufacturing and controls facilities are deemed acceptable. The review team recommends the NDA for **approval**.

### Life Cycle Considerations:

Two comparability protocols,  $(b) (4)$ , were proposed. They were evaluated by the DP and OPMA reviewers in consultation with the product quality review team in the Office of Life Cycle Drug Products (OLDP).

The applicant proposed a Comparability Protocol to  $(b) (4)$ . This is deemed not acceptable. The applicant revised the Comparability Protocol and proposed to  $(b) (4)$  for this change based on the Agency's feedback, which was found acceptable.

The applicant proposed another Comparability Protocol to  $(b) (4)$

The primary method for identification of drug product is HPLC and UV. The applicant agreed to  $(b) (4)$  the drug product

specification since (b) (4) per FDA's recommendation (reviewed by Yifan Wang and Bogdan Kurtyka in OPMA). The applicant indicated that they may (b) (4).

## 2. APPLICATION BACKGROUND

During the development of belzutifan, regulatory guidance on the design of MK-6482-001 and MK-6482-004 were obtained from the FDA. A summary of key interactions during the belzutifan clinical development program for the proposed indication is presented in [Table 1]. Quality/CMC related interactions are bolded in the first column.

**Table 1 Applicant – Summary of Key Interactions for Belzutifan Development**

Type of Meeting/Correspondence	Date	Purpose/Summary
Type B (EOP2) Meeting	10-JUN-2020	FDA DO1 provided advice on the development program for MK-6482 in the VHL disease-associated RCC indication and generally agreed with the registrational intent of MK-6482-004; requested the Sponsor to present the topline data before NDA submission.
Orphan Drug Designation Granted	24-JUN-2020	FDA OOPD granted ODD to MK-6482 in the indication of VHL disease; #DRU-2020-7458.
Request for Proprietary Name Review	2-JUL-2020 20-OCT-2020	The Applicant submitted request for proprietary name review. On 20-OCT-2020, FDA conditionally accepted the proposed proprietary name.
Type C CMC Meeting (WRO)	10-JUL-2020	FDA agreed with the Applicant's proposal on the choice of regulatory starting material for drug substance.
Breakthrough Therapy Designation Granted	23-JUL-2020	FDA DO1 granted BTB to MK-6482.
Pediatric Scientific Advice (Type F Meeting)	5-AUG-2020	FDA concurred with planned request for a waiver in the iPSP under FDARA.
Agreed PSP submission	30-OCT-2020	iPSP was prepared under FDARA requirements and submitted to FDA on 04-SEP-2020. Following FDA comments, the Applicant submitted the agreed PSP to FDA on 30-OCT-2020. In this PSP, the Applicant indicated the plan to request a waiver for pediatric development under FDARA.
Pre-Submission Meeting with CDRH Regarding VHL Testing	28-AUG-2020 29-SEP-2020	FDA CDRH informed the Applicant that VHL genetic testing needs to be developed as a Class II or a Class III device.
Type C CMC Meeting (WRO)	28-AUG-2020	FDA agreed with the 9-month stability data to support NDA submission and supplementation of 12-month stability data within ~ 60 days of NDA dossier submission completion.

Project Orbis	17-JUN-2020 25-SEP-2020 23-OCT-2020	<p>On 17-JUN-2020, FDA inquired about the Applicant's interests in participating in Project Orbis for the upcoming NDA submission.</p> <p>On 25-SEP-2020, the Applicant informed FDA of interest in participating in Project Orbis and proposed a submission plan regarding Project Orbis.</p> <p>On 23-OCT-2020, the Applicant provided an updated submission plan to FDA.</p>
Type B NDA Content/Format Meeting	23-OCT-2020	<p>The Applicant requested FDA advice regarding the NDA submission structure, content, format and schedule. The Applicant and FDA agreed upon:</p> <ul style="list-style-type: none"> <li>The Table of Content of the NDA submission.</li> <li>The Applicant's proposal of NDA rolling submission: Wave 1 (15-DEC-2020); Wave 2 (15-JAN-2021).</li> <li>Other submission schedules including CMC, Efficacy Update Report, Safety Update Report.</li> <li>Proposed structure of Integrated Summary of Safety, OSI deliverables.</li> </ul> <p>In addition, FDA requested the Applicant to submit a report and datasets regarding family history and diagnosis methods from Study MK-6482-004, and a report and datasets regarding pharmacogenetic analysis.</p>
Type B Pre-NDA Meeting	12-NOV-2020	<p>The Applicant presented topline results from the Study MK-6482-004 and requested FDA feedback on NDA submission, participation of RTOR pilot, and labeling.</p> <ul style="list-style-type: none"> <li>FDA agreed that: 1) NDA submission can proceed; 2) the Applicant's proposal on participating in the RTOR pilot; 3) AOM can be scheduled after NDA submission.</li> <li>FDA advised that labeling topic will be an NDA review issue.</li> <li>FDA agreed that a REMS is not likely for belzutifan. Final decision will be based on NDA review.</li> </ul> <p>FDA requested the Applicant to conduct multi-level analysis to estimate LGR from MK-6482-004 and requested a report and SAS program be submitted to support the review.</p>

		<p>FDA requested that multi-disciplinary and chemistry Assessment Aids should be submitted in Wave 2 (15-JAN-2021).</p> <p>FDA and the Applicant agreed that the food effect study should be conducted with the to-be-marketed formulation. The Applicant agreed to submit the summary of process changes between FMF and FMI to IND to facilitate FDA review.</p>
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### 3. SUMMARY OF CMC SPECIFIC PRESUBMISSION AGREEMENTS

Key CMC Interactions are summarized below in Table 2.

**Table 2 Applicant – Summary of Key CMC Interactions for Belzutifan Development**

Type of Meeting/ Correspondence	Date	Purpose/Summary
Type C CMC Meeting (WRO)	10-JUL-2020	FDA agreed with the Applicant's proposal on the choice of regulatory starting material for drug substance.
Type C CMC Meeting	28-AUG-2020	FDA agreed with the 9-month stability data to support NDA submission and supplementation of 12-month stability data within ~ 60 days of NDA dossier submission completion.
Type B Pre-NDA Meeting	12-NOV-2020	FDA and the Applicant agreed that the food effect study should be conducted with the to-be-marketed formulation. The Applicant agreed to submit the summary of process changes between FMF and FMI to IND to facilitate FDA review.

The FDA's Assessment: *Consistent with FDA's records*

### 4. ENVIRONMENTAL ASSESSMENT

The Applicant's Position:

The applicant is requesting a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.31(b). The production of the Active Pharmaceutical Ingredient, belzutifan, meets the requirements of a categorical exclusion under 21 CFR §25.31(b) because the estimated concentration of the drug substance at the point of entry, referred to as the Expected Introduction Concentration (EIC), into the aquatic environment will be below 1 part per billion (ppb). To the best of the firm's



**MSD International GmbH**  
Kilsheelan, Clonmel, Ireland

3002807560/  
985098317

Manufacture of Drug Product  
(b) (4)

Manufacture of Drug Product  
Drug Product Analytical Testing

Approved based  
on 704 (a)(4)  
Record Review in  
lieu of on-site  
inspection.

**Merck Sharp and Dohme  
Corp.**  
4633 Merck Road  
Wilson, NC USA

1036761/  
101740835

Drug Product Packaging (Primary  
and Secondary) and Labeling  
Drug Product Analytical Testing  
(Stability)

Approve Based on  
Previous History

(b) (4)

Drug Product Analytical Testing  
(Microbiological)

Approve Based on  
Previous History.

### The FDA's Assessment: *Adequate*

The drug product manufacturing site, MSD International GmbH, Ireland was considered high risk because the (b) (4) manufacturing process is new to the facility with no prior inspectional coverage. Therefore, a 704 (a)(4) document review was carried out in lieu of on-site inspection. Based on the joint 704a4 assessment between OPMA and ORA, the site is found adequate and recommended for approval. All other manufacturing facilities including the API manufacturing site, testing sites and primary packaging sites are found adequate based on prior history.

## 6. DRUG SUBSTANCE

### a. GENERAL DESCRIPTION AND STRUCTURE

Structure	
USAN Name	Belzutifan
IUPAC Name	3-{[(1S,2S,3R)-2,3-Difluoro-1-hydroxy-7(methanesulfonyl)-2,3-dihydro-1H-inden-4-yl]oxy}-5fluorobenzonitrile
Molecular Weight	383.34
Molecular Formula	C <sub>17</sub> H <sub>12</sub> F <sub>3</sub> NO <sub>4</sub> S
Solubility	0.010 mg/mL (Water) 59 mg/mL (Acetone) 38 mg/mL (Acetonitrile)
Polymorphism	No other crystal forms or (b) (4) exist.
pK <sub>a</sub>	Belzutifan has no functional groups that would be expected to have a pK <sub>a</sub> (in the range of 2 to 11)



The FDA's Assessment: *Adequate*

The provided information is sufficient for a small molecule. Belzutifan drug substance is a white to light brown powder. The molecule is manufactured as the free base. It has three chiral stereocenters and information on the optical rotation is provided in the submission. The selected polymorph is noted as (b) (4) and no other known crystal forms or (b) (4) were found from a polymorph screen. The drug substance is not hygroscopic. The solubility in water or other aqueous buffers is considered practically insoluble.

b. DRUG SUBSTANCE MANUFACTURING PROCESS

(b) (4)

69 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page



(b) (4)

## 8. BIOPHARMACEUTICS

### a. BCS CLASSIFICATION

Applicant to fill:

FDA assessment (FDA to fill):

*Conditionally Acceptable*

**BCS Classification:** BCS II

Choose an item.

Note that the applicant is not proposing formal FDA classification, but has classified belzutifan as BCS Class II based on the ICH guidance.

**FDA Comment/Assessment:**

The Reviewer agrees that (b) (4) belzutifan drug substance (b) (4) exhibits **low** solubility across the physiologic pH range. Additionally, based on the preliminary results of the *ongoing* human Mass Balance clinical study (MK-6482-008), belzutifan can potentially be categorized as a BCS-II (low solubility/high permeability) drug substance.

**Solubility of Drug Substance and (b) (4): Low**

The drug substance exhibits low solubility (~0.01 mg/mL at 25 °C) across the physiologic pH range, regardless of pH; refer to Table 1 of 3.2.S.1.

Note that during tablet manufacture, the drug substance is (b) (4)

Based on the equilibrium solubility data of belzutifan (b) (4) in various pH media at 25 °C (provided in SDN-6), it cannot be assured that at least 120 mg belzutifan (from the standard single dose of three 40 mg tablets, nor at least one 40 mg tablet) will completely dissolve in 250 mL pH buffer media at 37 °C.

**Permeability: Possibly High**

In SN-26, the Applicant confirmed that a Caco-2 permeability study was not conducted, but provided the location of the MDR1-MDCK and LLC-PK1 permeability study reports. In SN-33, the Applicant indicated that based on the preliminary results of the Mass Balance Study (PN008), it appears that >88% of belzutifan is systemically absorbed following single dose administration of a suspension of belzutifan (120 mg, 200 µCi) to 6 healthy subjects. The preliminary results of the human radiolabeled Mass Balance study currently provide support for the Applicant's claim of high permeability for belzutifan; however, a final determination will be made after receiving confirmation from the FDA Office of Clinical Pharmacology upon their review of the final clinical study report (targeted for submission in September/October 2021).

**Dissolution of Drug Product: Not Rapid Across the Entire Physiologic pH Range**

Belzutifan tablets exhibit very rapid (>85% in 15 min) dissolution using (900 mL volumes of) the proposed dissolution medium/method, and in pH 7.5 phosphate buffer medium, but exhibit incomplete (i.e., <30%) dissolution in water, 0.1N HCl, and pH 4.5 acetate buffer media.

**Additional Comments:**

The solubility of belzutifan when tested as the (b) (4) is higher in higher pH ( $\geq 6.0$ ) media as compared to in lower pH ( $\leq 4.0$ ) media. Additionally, the dissolution of belzutifan is faster/higher in higher pH (6.5 and 7.0) media. Per the FDA Clinical Pharmacology Reviewers, based on the results of an exploratory analysis, the apparently slightly higher exposure in patients who received gastric reducing agents (about 13% higher than the overall population and about 25% higher than the population in study 004) is not considered likely to drive a higher incidence of adverse reactions.

Additionally, since the number of patients included in the FDA exploratory analyses were not sufficient to isolate the effect of acid reducing agents, the data are considered limited to warrant related labeling recommendations at this time. For details, refer to the Clinical Pharmacology review.

The solubility of belzutifan (when tested as the (b) (4)) at 37 °C was also significantly higher in FaSSIF than FeSSIF (as shown in Table 2 of the IR Response in SN-26) which is consistent with the observation that concomitant administration of a high-fat, high-calorie meal delayed T<sub>max</sub> (by approximately 2 hours) and decreased C<sub>max</sub> by about 24% to 35%. However, since there was no significant change in belzutifan AUC, the proposed labeling states that the proposed drug product may be taken with and without food. The assessment of the acceptability of the proposed labeling statement related to food-effect is deferred to the FDA Clinical Pharmacology Reviewer.

#### b. DISSOLUTION TEST

[Applicant to fill]

USP Apparatus	Paddle Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
2	50 rpm	900 mL	37°C	50 mM potassium phosphate buffer at pH 6.5 with 68 mM potassium chloride	Q = (b) (4) % in 15 minutes

#### *Biopharmaceutics Figure 1: Dissolution as a function of:*

##### *a. Impact of medium pH on dissolution*

As a BCS Class II compound, belzutifan exhibits very low solubility at physiological pH (b) (4)

Dissolution of belzutifan (b) (4) is driven by the (b) (4)

A media pH of 6.5 was selected based on belzutifan (b) (4) solubility measurement experiments at different pH. The multi point dissolution profiles were performed using the tablets (b) (4)

Please refer to Module 3.3.1 for an overview of the dissolution figures.

(b) (4)	
FDA Comment: In SN-25, the Applicant indicated that the (b) (4) is used to manufacture belzutifan tablets. Information from the vendor indicates that (b) (4)	
<b>b. Impact of paddle Speed on dissolution</b> The applicant has only studied a paddle speed of 50 rpm for this program.	
FDA Comment: The Applicant's decision not to explore dissolution at higher paddle speeds is acceptable/reasonable.	
<b>c. Impact of other parameters on dissolution (add as appropriate)</b> The applicant has studied	
FDA Comment: N/A	
FDA Comment: N/A	
<b>d. Justification for selection of the acceptance criteria (or criterion)</b> Belzutifan is a rapidly dissolving oral tablet, and as such, the applicant has proposed, as per the FDA guidance, Q = (b) (4) % in 15 minutes.	
FDA Comment: Refer to the FDA Assessments of the Dissolution Method and Dissolution Acceptance Criteria below.	

	Applicant to fill:	FDA assessment:
The dissolution method is discriminating for:		
i) Particle size distribution (PSD) Link <sup>1</sup> : [Ref 3.3: 05GFQT]	Not applicable	Agree
ii) (b) (4)	Discriminating	Agree
iii) Formulation variations	Discriminating	Agree
iv) Manufacturing process variations	Discriminating	Agree
v) Other (specify):	Choose an item.	Not applicable

<sup>1</sup>The applicant to provide link to the appropriate section in the submission. FDA reviewer may update the link as needed.

**FDA Comments:****DISSOLUTION METHOD – Adequate***Justification of Chosen Dissolution Parameters*

The dissolution medium (pH 6.5 phosphate buffer) and added salt concentration (68 mM) were selected to achieve complete belzutifan dissolution within 45 minutes without sacrificing discriminating power, and to simulate small intestinal conditions (similar to FaSSIF media). (b) (4)

(b) (4); however, this Reviewer notes that the %RSD values appear to be highly similar in the presence and absence of added KCl. A paddle speed of 50 rpm did not result in coning of the test sample at the bottom of the vessel. The 900 mL medium volume was sufficient to achieve sink conditions during dissolution testing. Refer to Figures 1 and 4 of the [Dissolution Method Development Report/DMDR](#).

*Discriminating Power*

Based on the ability to reject intentionally manufactured variants with quality attributes different from the target product, it can be concluded that the proposed dissolution method is capable of discriminating for changes/differences in critical quality attributes including (1) tablet (b) (4) level, and (2) (b) (4) properties including (b) (4). Figure 5 of the DMDR shows that lower than target level of (b) (4) results in slower/lower dissolution profile; the profile similarity value ( $f_2$ ) for the (b) (4) (variant product) was <50 relative to the (b) (4) (target product). Additionally, there was >15% difference in dissolution values between the variant and target products, at sampling time points up to 20 min, suggesting dissimilarity of dissolution profiles. Figure 7 of the DMDR shows that the variant drug product lot manufactured using a (b) (4) outside the proven acceptable range (b) (4) did not exhibit very rapid dissolution. Per the Applicant, the (b) (4) is the main factor influencing (b) (4) (and thus tablet (b) (4) hardness).

Additionally, the Applicant provided data to show that the proposed dissolution method produces the correct rank-order relationship for variations in (3) (b) (4) content of (b) (4), (4) (b) (4) API content of the tablets, and (5) tablet hardness level; refer to the DMDR's Figures 6, 8, and 9, respectively. Based on the dissolution profile data provided for the target and variant drug products, larger-than-studied variations in (b) (4) content (<< (b) (4) %) and (based on the provided pH-solubility data of various (b) (4) in SN-25, also) a change in (b) (4) API (> (b) (4) %), and tablet hardness (>> (b) (4) kP) are necessary to be able to reject tablet lots using the proposed dissolution method. It is acknowledged that the studied ranges of these quality attributes may very well be within the product's design space, and additionally per the Applicant, (b) (4) on stability data demonstrated that the

(b) (4) API is maintained during long-term, accelerated, and 2-months of open-dish stress stability storage of the tablet. Based on this Reviewer's linear extrapolation analyses, tablet lots manufactured with (b) (4) with as low as (b) (4) % (b) (4) content is predicted to be rejected by USP Stage 2 (n=12) dissolution testing.

Additionally, based on the *in vitro* dissolution profile data of the target and variant products intentionally manufactured with (b) (4) (provided in Table 3 of the IR Response in SN-78), this Reviewer estimates via linear extrapolation that the proposed dissolution method will be able to reject by USP Stage 2 testing (n=12) products with (b) (4) starting as low as (b) (4) material. It is important to note that based on the preliminary results of the (b) (4) PK study (Study 019), drug products with up to (b) (4) will be bioequivalent (BE) to the product with (b) (4). Based on the 90% CI of the GMR data provided in the IR Response, this Reviewer predicts that lots containing (b) (4) API material will possibly be non-BE to the target product (i.e., at least in terms of plasma belzutifan C<sub>max</sub>), so overall, the proposed dissolution method is considered suitable in ensuring drug product performance with respect to (b) (4) drug content.

*Based on internal FDA discussions, the Biopharmaceutics Reviewer defers to (1) the Process Reviewer for the final determination regarding the acceptability of the proposed (b) (4), and the proposed average tablet hardness range ((b) (4) kP – (b) (4) kP), (2) the Drug Product Reviewer for the final determination regarding the acceptability of the proposed (b) (4) content (i.e., (b) (4) % – (b) (4) %), as well as the decision regarding whether the (b) (4) needs to be specified in 3.2.P.1 Description and Composition of the Drug Product, and (3) the Drug Product and Process Reviewers for the assessment of the Applicant's proposal not to include a QC test for presence/level of (b) (4) API in the (b) (4) product and finished product QC specifications.*

During processing of the (b) (4). Per the Applicant, (b) (4) have been identified. Thus, this Reviewer agrees that (b) (4) API's particle size distribution is likely not a critical quality attribute affecting dissolution of the belzutifan tablets.

#### *Analytical Method Validation*

HPLC with UV detection at 233 nm is used to quantify belzutifan in the dissolution samples. Using a Design of Experiment (DoE) experimental study approach, the dissolution method was reported to be robust with respect to paddle speed ( $50 \pm 2$  rpm), bath temperature ( $37 \pm 1$  °C), buffer salts concentration ((b) (4)  $\pm 5\%$ ; (b) (4)  $\pm 5\%$ ), KCl concentration ((b) (4)  $\pm 5\%$ ), i.e., because all dissolution datapoints were within  $\pm 3\%$  of the nominal target value; refer to Table 13 of 3.2.P.5.3.2 Analytical Method Validation. Additionally, based on the results of a one-factor-at-a-time (OFAT) study, the dissolution method was considered robust with respect to presence/absence of deaeration of dissolution medium. Furthermore, the 30-minute dissolution data values using manual and automatic sampling methods were



reported to be comparable, and the chosen filtration technique (10 µm full flow filter followed 0.45 µm hydrophilic PTFE filter, with at least the first 2 mL filtrate discarded) was reported to be compatible with the dissolution samples. The sample solutions were reported to be stable for at least 5 days at ambient storage conditions. Per the Drug Product Reviewer, the analytical method validation for dissolution is acceptable.

#### *Sink conditions*

Given that when tested as (b) (4) the reported equilibrium belzutifan solubility at ambient temperature is 130 mcg/mL, and the reported belzutifan solubility in the proposed dissolution medium (50 mM potassium phosphate buffer at pH 6.5 with 68 mM potassium chloride) at 37 °C is 429 mcg/mL, approximately sink or greater than sink conditions are anticipated to be achieved and maintained during dissolution testing in 900 mL of the proposed QC dissolution medium at 37 °C. For the solubility data of belzutifan (tested as (b) (4)) in the proposed QC dissolution medium, refer to the Applicant's Response to the Quality IR in SDN-6.

#### **DISSOLUTION ACCEPTANCE CRITERIA – Adequate**

Based mainly on the dissolution profile data of the FMF tablets that were evaluated in the pivotal Phase 2 clinical trial (and the FMI lots evaluated in clinical studies), as well as ability to reject tablet batches with unacceptable quality attributes, the proposed dissolution acceptance criterion ( $Q = \frac{(b)}{(4)}\%$  at 15 min) is acceptable for QC of belzutifan tablets at batch release and during shelf-life/stability testing. Note that the FMF tablet is qualitatively and quantitatively (Q1/Q2) compositionally the same as the proposed to-be-marketed FMI tablets.

Additionally, a single-point dissolution acceptance criterion is deemed sufficient by this Reviewer based on the following observations: (1) Using the proposed dissolution method, belzutifan tablet exhibits very rapid dissolution which justified the dissolution specification time point of 15 minutes for " $Q = \frac{(b)}{(4)}\%$ ". (2) Even though belzutifan is a low solubility drug substance per BCS criteria, (b) (4)

effectively enhances drug substance solubility and bioavailability of the proposed immediate release tablets. (3) The CDER-QT-IRT Team confirmed that belzutifan tablets does not produce large mean increases in the QT interval at the recommended dose. (4) The Applicant states that based on exposure-response analysis, drug exposures are possibly associated with greater therapeutic benefit, and thus most high exposure scenarios would not require dose adjustment for safety. Thus, a second/earlier specification with an *upper* tolerance limit is likely not needed. (5) Additionally, an earlier specification time point with a *lower* tolerance limit is also likely not needed. The Clinical Pharmacology Reviewer (Dr. Salaheldin Hamed) confirmed that the observed ~35% and ~24% lower belzutifan C<sub>max</sub> from concomitant administration of a high-fat meal with the pivotal clinical trial FFP/O<sub>(b) (4)</sub>T formulation and the proposed commercial FMI tablet, respectively do not warrant restricting administration of the proposed drug product with regard to meals. Similarly, the ~13% lower C<sub>max</sub> from another pivotal

clinical trial formulation (i.e., FMF/FCT) relative to the FFP/O<sup>(b)</sup><sub>(4)</sub>T formulation is not a concern because efficacy correlates with belzutifan AUC.

#### *Dissolution on Stability*

Based on 12 months of long-term (25°C/60%RH) and 6 months of accelerated (40°C/75%RH) stability data of the three Formal Stability Study (FSS) lots of the packaged FMF/FCT tablets (including dissolution profile data generated using the proposed dissolution method), the proposed expiration dating period for the proposed drug product is 24 months when stored at 20 - 25°C. This Reviewer confirms the Applicant's conclusion that no apparent dissolution on stability trends were observed, and the FSS stability lots conformed to the Applicant's proposed dissolution acceptance criterion during the stability study period.

Like the FMF/FCT (FSS) tablet lots, the six Commercial Site Stability lots representing the FMI tablet are very rapidly dissolving at the initial stability time point. Based on the updated dissolution on stability data for the proposed commercial (FMI) drug product lot being evaluated in the commercial site stability study, there also appears to be no dissolution on stability trend with the proposed to-be-marketed (FMI tablet) drug product, and no evidence of inability to conform to the proposed dissolution acceptance criterion ( $Q = \text{(b)}_{(4)}\%$  at 15 minutes) over the 6 months of accelerated and long-term stability testing period.

### c. BRIDGING THROUGHOUT DRUG PRODUCT DEVELOPMENT (FORMULATION, PROCESS, OR SITE CHANGE)

With respect to formulation changes, the applicant refers FDA to Module 2.7.1, which describes the changes to the formulation, and the bridging study conducted to support the change.

With respect to process changes, the applicant refers FDA to the pre-NDA meeting outcome, where the applicant provided FDA with the process change overview and our justification for bridging the changes (IND 132,120 SN0102 and IND 137,354 SN0069). This information is also present in the 3.2.P.2.3 section.

With respect to site changes, data to support the commercialization site ability to manufacture product is provided in Section 3.2.P.5.4.

In addition, the applicant refers the reviewer to Section 3.3.2, Investigational Formulations, which details specific batches and formulation used in each of the clinical studies.

[Sec. 2.7.1]

Page#:

[Sec. 3.2.P.5.4-6482-tablet]

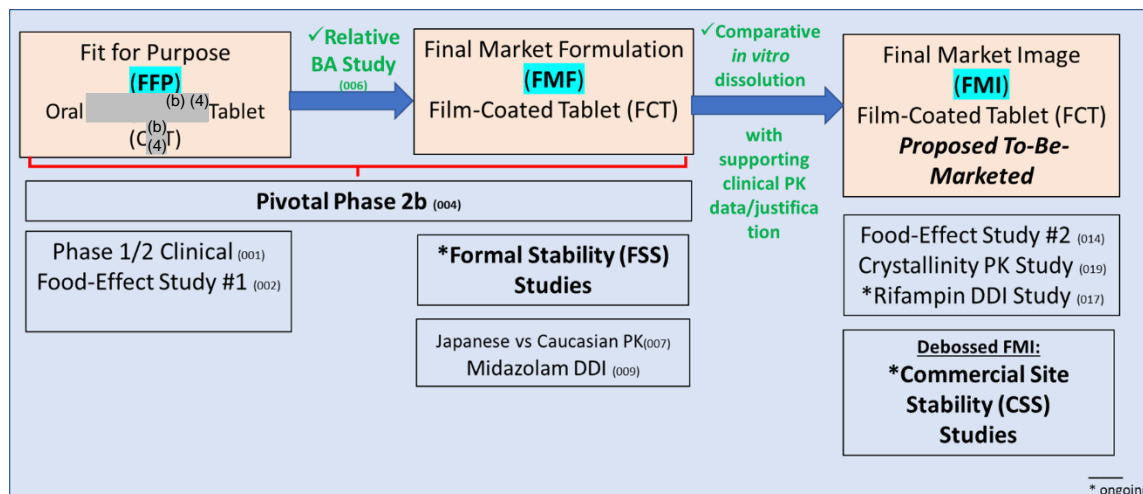


[Ref 3.3: 05FP3F]

The FDA's Assessment: *Adequate*

[FDA will complete this section.]

The bridging of the three formulations/products used during pharmaceutical and clinical development of belzutifan tablets is summarized in the diagram below.



Bridging to the Final Market Image (FMI) Tablets:

The proposed to-be-marketed final market image/FMI tablet differs from the final market formulation tablet (FMF) used in pivotal Phase 2 and other clinical studies in terms of (i) (b)(4) some or all portions of three excipients (b)(4) without a change in the total formulation qualitative & quantitative (Q1/Q2) composition, (ii) the drug substance/API, (b)(4), and finished drug product manufacturers, and (iii) the presence/absence of debossing on the tablet coating. CMC data were provided in the original NDA for one FMI/CSS tablet lot (0001157539) that was produced with the proposed commercial batch size range (b)(4) kg vs. (b)(4) kg by the proposed commercial (b)(4) and drug product manufacturer (MSD/Ireland) using the drug substance from the proposed commercial API supplier (b)(4), and the proposed commercial packaging configuration (90-count HDPE bottles with desiccant). In SN-70, batch release data were provided for additional commercial scale/site FMI tablet lots (e.g., 0001203109) that were used in clinical studies.

Overall, the available *in vitro* dissolution profile data and additional clinical (PK) information (for the three formulations) support the comparability of the FMF and the FMI tablets. The following observations support this conclusion.



- d) In SN-70, the Applicant provided comparative PK data that *confirms* the overall similarity of the FFP, FMF, and FMI tablets in terms of belzutifan C<sub>max</sub> and AUC, as well as PK profiles achieved in healthy subjects and patients.
- e) In SN-85, the Applicant provided additional comparative *in vitro* dissolution profile data to demonstrate the similarity of the unmarked FMI tablet (used in clinical studies) and the debossed final proposed to-be-marketed FMI tablet (used in commercial site stability studies).
3. A comparison of the *in vitro* dissolution on stability data of the FMI/CSS lot 0001157539 and FMF (Phase 2 clinical and Formal Stability Study/FSS) tablet lot (i.e., CDPMG) indicates no observed storage-time dependent trends. Clinical/FSS Lot CDPMG was manufactured within the proposed commercial batch size range ((b) (4) kg vs. (b) (4) kg) by (b) (4) using (b) (4) (b) (4) from API supplied by (b) (4). FMF Lot CDPMG and the other two primary registration lots (CDPMF and CDPMH with the same DS and DP manufacturers) have to up 12 months of long-term and up to 6 months of accelerated (dissolution profile) on stability data, i.e., generated using the proposed dissolution method, whereas the CSS lot has up to 6 months of stability data. Based on the 6 months stability data of the proposed commercial site stability lot (Batch 0001157539) there was no change in dissolution profiles during long-term and accelerated storage. Based on the stability data for three formal stability study (FSS) lots of the FMF tablets manufactured by (b) (4) a using API from three suppliers ((b) (4)), there was also no apparent trend in dissolution profiles during stability testing of the FMF tablets.
4. Furthermore, the FDA CMC Review Team concluded that overall, the API supplier, and drug product manufacturing process/site differences between the pivotal clinical/formal stability studies and the clinical/commercial site stability/to-be-marketed products were minor and thus, a dedicated *in vivo* BE study with the FMF/FSS versus FMI/CSS tablets would not be warranted. The Process and Drug Product Reviewers (Drs. Md Abdullah Mahmud and Dr. Nina Ni, respectively) confirmed that the process/facilities differences between the FMF and the FMI tablets are not considered major CMC changes. Specifically, the in-process change involving the (b) (4) does not involve a change in the core tablet composition, and thus is a minor process change (equivalent to a level 1 or 2 per SUPAC-IR Guidance), and (2) the equipment in the two manufacturing sites are of the same design, same operating principles with same controls. Similarly, the Drug Substance Reviewer (Dr. Rajan Pragani) confirmed that the drug substance process changes from the clinical to the proposed commercial phases were considered minor, as evidenced by the apparently comparable impurity profiles of API from different suppliers. Additionally, per the Drug Substance

Reviewer, the stability data from the DS commercial supplier (b) (4)  
(provided in SDN-21) support (b) (4)-month retest period.

*In Vivo Bridging of Pivotal Clinical Trial Formulations (FMF/FCT vs. FFP/O<sup>(b) (4)</sup>T):*  
Bioequivalence (BE) Study 006 compared the *in vivo* PK profiles of the Fit-for-Purpose/Oral (b) (4) Tablet (FFP/O<sup>(b) (4)</sup>T) and the Final Marketing Formulation/Film-Coated Tablet (FMF/FCT) formulations; the adequacy of the clinical PK bridge between these two clinical formulations was confirmed by the FDA Clinical Pharmacology Reviewer. The FFP/O<sup>(b) (4)</sup>T and the FMF/FCT were both used in Phase 2 and other clinical (PK, efficacy/safety) studies including BE Study 006. Note that the compositions of FFP/O<sup>(b) (4)</sup>T and FMF/FCT are not qualitatively the same, so comparative *in vitro* dissolution profile data were not considered to support formulation bridging.

#### d. BIOWAIVER REQUEST

The Applicant's Position:

The NDA does not contain a biowaiver request.

The NDA does not contain a biowaiver request.

*Link:*

Page#:

[To the Applicant: Insert text here]

The FDA's Assessment: *Not Applicable*

[FDA will complete this section.]

#### e. DATA TO SUPPORT IVIVC AND/OR PBBM MODELING, IF APPLICABLE.

Not applicable.

The FDA's Assessment: *Not Applicable*

[FDA will complete this section.]



## 9. LABELING

### USPI

Highlights: *Adequate*

TRADEMARK™ (belzutifan) tablets, for oral use  
Initial U.S. Approval: XXXX

#### -----DOSAGE FORMS AND STRENGTHS-----

- Tablets: 40 mg (3)

Section 2 (if relevant): *Not Applicable*

Section 3 Dosage Forms and Strengths: *Adequate*

### 3 DOSAGE FORMS AND STRENGTHS

Tablets: 40 mg, blue, oval shaped, film-coated, debossed with "177" on one side and plain on the other side.

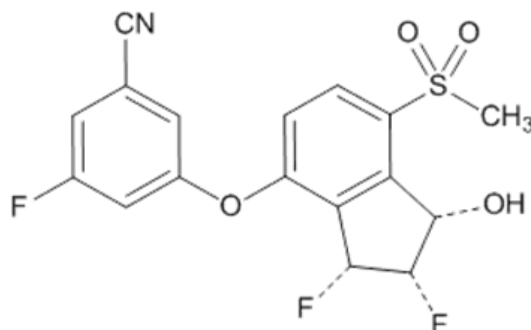
Section 11 Description: *Adequate*

If the following excipients used in the drug product, include warning/declaration in the USPI:

- FD&C Yellow No.5 or No.6, as a color additive (21 CFR 201.20) is not used.
- Phenylalanine, as a component of aspartame (21 CFR 201.21) is not used.
- Sulfites (21 CFR 201.22) is not used.

## 11 DESCRIPTION

Belzutifan is an inhibitor of hypoxia-inducible factor-2 $\alpha$  (HIF-2 $\alpha$ ). The chemical name of belzutifan is 3-[[[(1S,2S,3R)-2,3-Difluoro-2,3-dihydro-1-hydroxy-7-(methylsulfonyl)-1H-inden-4-yl]oxy]-5-fluorobenzonitrile. The molecular formula is C<sub>17</sub>H<sub>12</sub>F<sub>3</sub>NO<sub>4</sub>S and the molecular weight is 383.34 Daltons. The chemical structure is:



Belzutifan is a white to light brown powder that is soluble in acetonitrile, dimethoxyethane, and acetone, sparingly soluble in ethyl acetate, very slightly soluble in isopropanol and toluene, and insoluble in water.

TRADEMARK is supplied as blue, film-coated tablets for oral use containing 40 mg of belzutifan together with croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, mannitol, microcrystalline cellulose, and silicon dioxide as inactive ingredients. In addition, the film-coat contains FD&C Blue #2 aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide.

Section 16 How Supplied/Storage and Handling: **Adequate**

### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### How Supplied

TRADEMARK tablets are supplied as (b) (4) 40 mg blue, oval shaped, film-coated (b) (4) debossed with "177" on one side and plain on the other side, available in:

- bottles of 90 tablets with child-resistant closure: NDC 0006-5331-01.

The bottle also contains two desiccant canisters. Do not eat.

#### Storage and Handling

Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F) [see USP Controlled Room Temperature].

Manufacturer Information (Name and Address): **Provided: Adequate**

### Carton/Container Label **Adequate**

There is no carton label provided which was conveyed to the DMEPA at the first labeling meeting on 04/13/2021. The following comments were conveyed to the applicant, dated 07/26/2021:

- Add "Do not use if safety liner/inner seal is broken or missing."
- Delete (b) (4) in front of 59°F.

The applicant updated the container label accordingly in the Amendment, SDN 0086, dated 07/27/2021, which deems adequate. The updated label was copied below:



(b) (4)



## Final Risk Assessments

[FDA will complete this section.]

**To the Review Team:** Keep the appropriate Table; delete the rest

### SOLID ORAL

Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay, stability	<ul style="list-style-type: none"><li>• Formulation</li><li>• Container closure</li><li>• Raw materials</li><li>• Process parameters</li><li>• Scale/equipment</li><li>• Site</li></ul>	Low	Adequate control is in place. See evaluation on Section 7d.	Low	
Physical stability (solid state)	<ul style="list-style-type: none"><li>• Formulation</li><li>• Raw materials</li><li>• Process parameters</li><li>• Scale/equipment</li><li>• Site</li></ul>	Medium	Adequate control is in place. See evaluation on Section 7d.	Low	
Content Uniformity	<ul style="list-style-type: none"><li>• Formulation</li><li>• Container closure</li><li>• Raw material</li><li>• Process Parameters</li><li>• Scale/equipment</li><li>• Site</li></ul>	Medium	(b) (4) See evaluation on Section 7a.	Low	
(b) (4)	<ul style="list-style-type: none"><li>• Formulation</li><li>• Container closure</li><li>• Process parameters</li><li>• Scale/equipment</li><li>• Site</li></ul>	Low	Adequate control is in place. See evaluation on Section 7d.	Low	
Microbial Limits	<ul style="list-style-type: none"><li>• Formulation</li><li>• Raw materials</li><li>• Process parameters</li><li>• Scale/equipment</li><li>• Site</li></ul>	Low	Adequate control is in place. See evaluation on section 7d.	Low	
Dissolution – BCS Class II & IV	<ul style="list-style-type: none"><li>• Formulation</li><li>• Container Closure</li><li>• Raw materials</li><li>• Process parameters</li><li>• Scale/equipment</li><li>• Site</li></ul>	Medium	Adequate dissolution method; see section 8b.	Low	

## Recommendation Page

[FDA will complete this section.]

### ***Drug Substance: Approval***

Primary Reviewer: Rajan Pragani  
Secondary Reviewer: Paresma Patel

Date: July 22, 2021  
Date: July 22, 2021

### ***Drug Product: Approval***

Primary Reviewer: Nina Ni  
Secondary Reviewer: Anamitro Banerjee

Date: June 23, 2021  
Date: June 23, 2021

### ***Process and Facility: Approval***

Primary Reviewer: Md Abdullah Al Mahmud  
Secondary Reviewer: Rakhi Shah

Date: July 13, 2021  
Date: July 13, 2021

### ***Biopharmaceutics: Approval***

Primary Reviewer: Gerlie Gieser, Ph.D.  
Secondary Reviewer: Banu Zolnik, Ph.D.

Date: July 15, 2021  
Date: July 15, 2021

### ***Application Technical Lead: Approval***

Xiao Hong Chen

Date: July 28, 2021

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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XIAOHONG CHEN  
07/28/2021 07:00:36 PM

RAJAN PRAGANI  
07/29/2021 07:07:51 AM

PARESMA R PATEL  
07/29/2021 07:12:32 AM

NINA NI  
07/29/2021 08:58:46 AM

ANAMITRO BANERJEE  
07/29/2021 09:02:49 AM

MD ABDULLAH A MAHMUD  
07/29/2021 09:06:19 AM

RAKHI B SHAH  
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GERLIE GIESER  
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BANU S ZOLNIK  
07/29/2021 10:28:38 AM